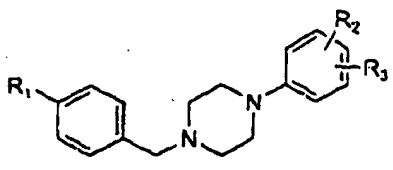




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(21) International Application Number: PCT/US98/01628 (22) International Filing Date: 29 January 1998 (29.01.98) (30) Priority Data: 08/791,673 30 January 1997 (30.01.97) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 08/791,673 (CON) Filed on 30 January 1997 (30.01.97) (71) Applicant (for all designated States except US): NEUROGEN CORPORATION [US/US]; 35 N.E. Industrial Boulevard, Branford, CT 06405 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): THURKAUF, Andrew [US/US]; 16 Fox Den Road, Danbury, CT 06811 (US). CHEN, Xi [US/US]; 144 East Main Street, Clinton, CT 06413 (US). (74) Agent: SARUSSI, Steven, J.; McDonnell Bochnen Hulbert & Berghoff, 300 South Wacker Drive, Chicago, IL 60606 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: 1-PHENYL-4-BENZYLPIPERAZINES: DOPAMINE RECEPTOR SUBTYPE SPECIFIC LIGANDS (D4) <div style="text-align: center; margin: 20px 0;">  <div style="position: absolute; left: 740px; top: 570px;">(I)</div> </div> (57) Abstract <p>Disclosed are compounds of formula (I) or the pharmaceutically acceptable addition salts thereof wherein: R₁ is halogen or C₁-C₄ alkyl; and R₂ and R₃ are the same or different and represent hydrogen, halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, alkylthio, hydroxy, amino, mono(C₁-C₄)alkylamino, di(C₁-C₄)alkylamino, or R₂ and R₃ together represent a 4 carbon alkenylene moiety that together with the phenyl ring to which they are attached form a naphthyl moiety, which compounds are dopamine D₄(ant)agonists and useful in the treatment of neuropsychological diseases such as schizophrenia, psychotic depression and mania.</p>		

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1-PHENYL-4-BENZYLPIPERAZINES: DOPAMINE RECEPTOR SUBTYPE SPECIFIC LIGANDS (D4)

BACKGROUND OF THE INVENTION

5

Field of the Invention

This invention relates to certain 1-phenyl-4-benzylpiperazines and pharmaceutical compositions containing them. It also relates to the use of such compounds in the treatment or prevention of psychotic disorders such as schizophrenia and other central nervous system diseases. The use of the compounds of this invention to the treatment of these disorders is indicated by the ability of the compounds to bind selectively to dopamine receptor subtypes.

Description of the Related Art

The therapeutic effect of conventional antipsychotics, known as neuroleptics, is generally believed to be exerted through blockade of dopamine receptors. However, neuroleptics are frequently responsible for undesirable extrapyramidal side effects (EPS) and tardive dyskinesias, which are attributed to blockade of D2 receptors in the striatal region of the brain. The dopamine D4 receptor subtype has recently been identified (Van Tol, H. H. et al., *Nature*, 1991, 350, 610). Its unique localization in limbic brain areas and its differential recognition of various antipsychotics suggest that the D4 receptor play a role in the etiology of schizophrenia. Selective D4 antagonists are effective antipsychotics free from the neurological side effects displayed by conventional neuroleptics.

Since dopamine D4 receptors are concentrated in the limbic system which controls cognition and emotion, compounds which interact with these receptors have utility in the treatment of cognitive disorders. Such disorders include the cognitive deficits which are a significant component of the negative symptoms (social withdrawal and unresponsiveness) of schizophrenia. Other disorders involving memory impairment or attention deficit disorders can also be treated with compounds that interact specifically with the dopamine D4 receptor subtype.

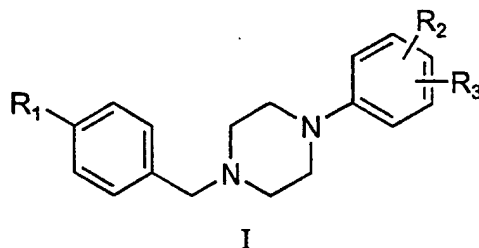
Japanese patent JP 47017306 discloses m-trifluoromethylphenyl benzyl piperazines as tranquilizers and analgetic agents. Nucl. Med. Biol. 20(6), 777-94, 1993, discloses radiolabelled 1-([4-{fluoro-18F}phenyl]methyl)-4-(3-[trifluoromethyl]phenyl)piperazine as an imaging agent.

J. Med. Chem. 37, 1060-1062, 1994, and International Application No. WO 9304684 discloses 4-arylpiperazines and 4-arylpiperidines.

J. Med. Chem. 11, 1144-1150, 1968, discloses certain 1-phenyl-4-benzyl piperazines as antihypertensive agents.

SUMMARY OF THE INVENTION

This invention provides novel compounds of Formula I which interact with dopamine receptor subtypes. Accordingly, a broad embodiment of the invention is directed to a compound of Formula I:



or the pharmaceutically acceptable addition salts thereof wherein:

R₁ is halogen or C₁-C₄ alkyl; and

R₂ and R₃ are the same or different and represent hydrogen, halogen, C₁-C₄ alkyl, C₁-C₄ alkoxy, alkylthio, hydroxy, amino, mono(C₁-C₄)alkylamino, di(C₁-C₄)alkylamino, or
 10 R₂ and R₃ together represent a 4 carbon alkenylene moiety that together with the phenyl ring to which they are attached form a naphthyl moiety.

The compounds of the present invention demonstrate high affinity and selectivity in
 15 binding to the Dopamine D4 receptor subtype. Consequently, they are useful in the treatment of schizophrenia, psychotic depression and mania. Other dopamine-mediated diseases such as Parkinsonism and tardive dyskinesias can also be treated directly or indirectly by modulation of D4 receptors. Compounds of the invention are also useful in treating the extrapyramidal side effects associated with the use of conventional neuroleptic agents as well as in the
 20 treatment of other disorders which respond to dopaminergic blockade such as substance abuse and obsessive compulsive disorder.

Furthermore, compounds of this invention are useful in treating depression, memory-impairment or Alzheimer's disease by modulation of D4 receptors which selectively exist in limbic areas known to control emotion and cognitive functions. The interaction of 1-phenyl-
 25 4-benzylpiperazines with dopamine receptor subtypes is shown. This interaction results in the pharmacological activities of these compounds.

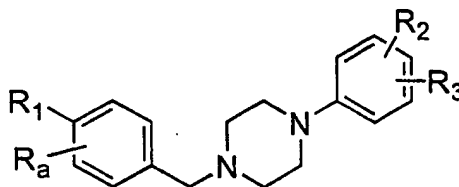
The invention further provides pharmaceutical compositions comprising compounds of Formula I. It also relates to the use of such compounds and compositions in the treatment and/or prevention of neuropsychological disorders including, but not limited to,
 30 schizophrenia, mania, dementia, depression, anxiety, dystonia, compulsive behavior,

substance abuse, memory impairment, cognitive deficits, Parkinson-like motor disorders and motion disorders related to the use of neuroleptic agents.

DETAILED DESCRIPTION OF THE INVENTION

As mentioned above, the invention encompasses substituted 1-Phenyl-4-benzylpiperazines of formula I. Preferred compounds of formula I are those where R_2 and R_3 may not be 2-isopropoxyl and hydrogen, respectively, when R_1 is bromo.

5 The invention also provides compounds of formula IA:



IA

or the pharmaceutically acceptable acid salts thereof wherein:

R_1 is halogen or C_1 - C_4 alkyl, and R_a is hydrogen; or

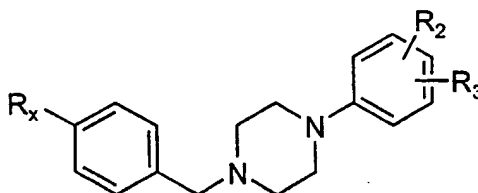
10 R_1 and R_a together represent $C_{3,5}$ alkylene containing one or two oxygen atoms which together with the phenyl group forms a five- or six-membered ring containing one or two oxygen atoms;

R_2 and R_3 are the same or different and represent hydrogen, halogen, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, alkylthio, hydroxy, nitro, amino, monoalkylamino or dialkylamino, or

15 R_2 and R_3 together represent $C_{3,5}$ alkylene or alkenylene containing one or two oxygen atoms which together with the phenyl form a five- or six-membered ring substituted with one or two oxygen atoms,
with the proviso that R_2 and R_3 may not be 2-isopropoxyl and hydrogen respectively when R_1 is bromo.

20

The invention also encompasses compounds of formula II:



II

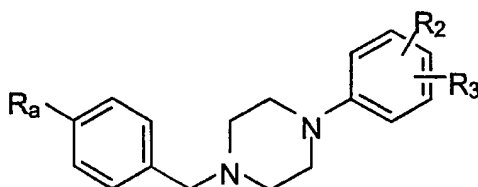
25 wherein

R_x is fluorine, chlorine, bromine, or iodine; and

R_2 and R_3 are the same or different and represent hydrogen, halogen, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, alkylthio, hydroxy, amino, monoalkylamino or dialkylamino.

In preferred embodiments of formula II, R_2 and R_3 may not be 2-isopropoxyl and hydrogen, respectively, when R_1 is bromo. More preferred compounds of formula II are those where R_1 is chloride; R_2 and R_3 may not be 2-isopropoxyl and hydrogen, respectively, when R_1 is bromo; R_2 is halogen, most preferably chloride, or methyl or methoxy; and R_3 is hydrogen or methyl.

The invention also encompasses compounds of formula III:



III

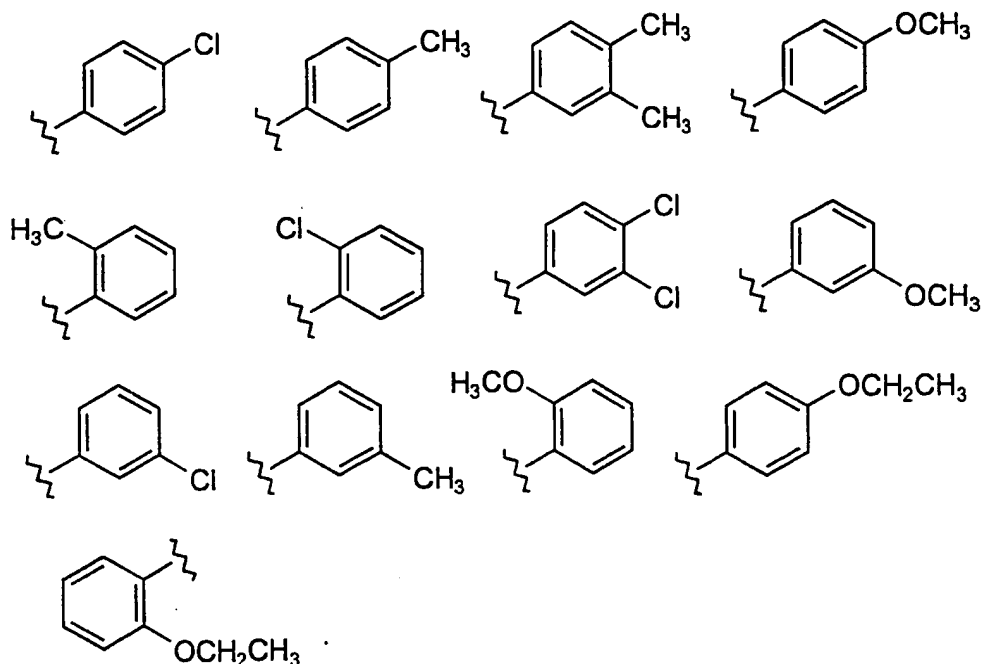
wherein

R_a is C_1 - C_4 alkyl; and

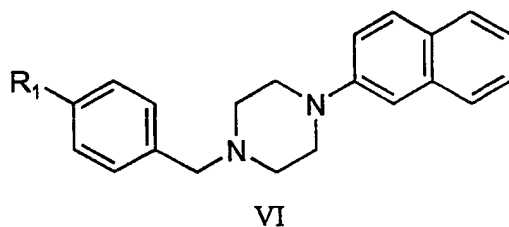
R_2 and R_3 are the same or different and represent hydrogen, halogen, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, alkylthio, hydroxy, amino, monoalkylamino or dialkylamino.

In preferred embodiments of formula III, R_a is methyl; R_2 is halogen, most preferably chloride, or methyl or methoxy; and R_3 is hydrogen or methyl.

Particularly preferred compounds of formulas II and III are those where the phenyl group substituted with R_2 and/or R_3 is selected from the group consisting of:



The invention also encompasses compounds of formula VI:



wherein

R₁ is C₁-C₄ alkyl or halogen.

Preferred compounds of formula VI are those where R₁ is methyl, Cl, or F.

The invention also encompasses a method for treating or preventing neuropsychological disorders such as, for example, schizophrenia and other central nervous system diseases which comprises administering to a patient in need of such treatment a compound of the invention.

Representative compounds of the present invention, which are encompassed by Formula I, include, but are not limited to the compounds in Table I and their pharmaceutically acceptable salts. Non-toxic pharmaceutically acceptable salts include salts of acids such as hydrochloric, phosphoric, hydrobromic, sulfuric, sulfinic, formic, toluenesulfonic, methanesulfonic, nitric, benzoic, citric, tartaric, maleic, hydroiodic, alcanoic such as acetic,

HOOC-(CH₂)_n-COOH where n is 0-4, and the like. Those skilled in the art will recognize a wide variety of non-toxic pharmaceutically acceptable addition salts.

The present invention also encompasses the acylated prodrugs of the compounds of Formula I. Those skilled in the art will recognize various synthetic methodologies which may be employed to prepare non-toxic pharmaceutically acceptable addition salts and acylated prodrugs of the compounds encompassed by Formula I.

By the terms C₁-C₄ alkyl and lower alkyl is meant straight and branched chain alkyl groups having from 1-4 carbon atoms as well as cyclic alkyl groups such as, for example, cyclopropyl and cyclobutyl. Specific examples of such alkyl groups are methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, and sec-butyl. Preferred C₁-C₄ alkyl groups are methyl and ethyl.

By the terms C₁-C₄ alkoxy and lower alkoxy is meant straight and branched chain alkoxy groups having from 1-4 carbon atoms.

By the term alkylthio is meant lower alkyl groups bound to the parent system, e.g., a phenyl group, by a sulfur atom.

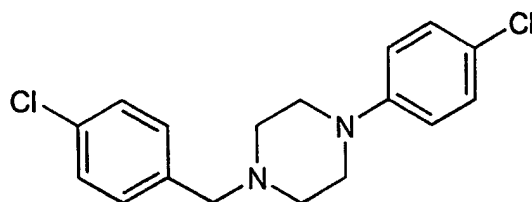
By halogen, halo, or halide is meant fluorine, chlorine, bromine and iodine substituents.

Where R₂ and R₃ together represent C_{3,5} alkylene or alkenylene containing one or two oxygen atoms which together with the phenyl form a five- or six-membered ring substituted with one or two oxygen atoms, the resulting groups include the following:

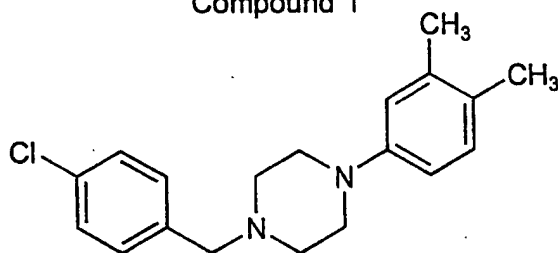


Representative examples of compounds according to the invention are shown in Table 1 below.

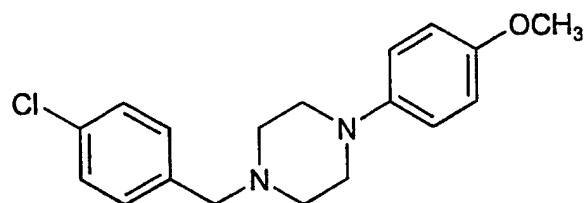
Table 1



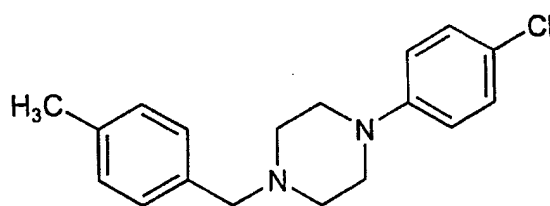
Compound 1



Compound 2



Compound 3



Compound 4

5

The pharmaceutical utility of compounds of this invention are indicated by the following assays for dopamine receptor subtype affinity.

Assay For D2 and D4 Receptor Binding Activity

10 Pellets of COS cells containing recombinantly produced D2 or D4 receptors from human are used for the assays. The sample is homogenized in 100 volumes (w/vol) of 0.05 M Tris HCl buffer at 4° C and pH 7.4. The sample is then centrifuged at 30,000 x g and resuspended and rehomogenized. The sample is then centrifuged as described above and the

final tissue sample is frozen until use. The tissue is resuspended 1:20 (wt/vol) in 0.05 M Tris HCl buffer containing 100 mM NaCl.

Incubations are carried out at 48°C and contain 0.4 ml of tissue sample, 0.5 nM 3H-YM 09151-2 and the compound of interest in a total incubation mixture of 1.0 ml.

5 Nonspecific binding is defined as that binding found in the presence of 1 mM spiperone; without further additions, nonspecific binding is less than 20% of total binding. Representative binding characteristics for compounds of the invention for the D2 and D4 receptor subtypes are shown in Table 2 for cloned human dopamine receptors. Typically, the compounds of the invention have similar binding profiles.

10 Table 2

Compound Number	D4 Ki (nM)	D2 Ki (nM)
1	5	>1000
15 2	16	>600
3	5	>1000
4	15	>300

Compound numbers relate to compounds described below in the examples.

20 The compounds disclosed in Japanese patent JP 47017306 and Nucl. Med. Biol. 20(6), 777-94, 1993 were prepared and tested using the above assay. Those compounds did not selectively bind to dopamine subtypes.

25 The compound disclosed in J. Med. Chem. 11, 1144-1150, 1968, as Compound 97, i.e., a 4-methoxy derivative, was prepared and found to not selectively bind to dopamine subtypes.

30 The compounds of general formula I may be administered orally, topically, parenterally, by inhalation or spray or rectally in dosage unit formulations containing conventional non-toxic pharmaceutically acceptable carriers, adjuvants and vehicles. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection or infusion techniques. In addition, there is provided a pharmaceutical formulation comprising a compound of general formula I and a pharmaceutically acceptable carrier. One or more compounds of general formula I may be present in association with one or more non-toxic pharmaceutically acceptable carriers and/or diluents and/or adjuvants and if

desired other active ingredients. The pharmaceutical compositions containing compounds of general formula I may be in a form suitable for oral use, for example, as tablets, troches, lozenges, aqueous or oily suspensions, dispersible powders or granules, emulsion, hard or soft capsules, or syrups or elixirs.

5 Compositions intended for oral use may be prepared according to any method known to the art for the manufacture of pharmaceutical compositions and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavoring agents, coloring agents and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets contain the active ingredient in admixture with non-toxic
10 pharmaceutically acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example, corn starch, or alginic acid; binding agents, for example starch, gelatin or acacia, and lubricating agents, for example magnesium stearate, stearic acid or talc. The
15 tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed.

 Formulations for oral use may also be presented as hard gelatin capsules wherein the
20 active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or as soft gelatin capsules wherein the active ingredient is mixed with water or an oil medium, for example peanut oil, liquid paraffin or olive oil.

 Aqueous suspensions contain the active materials in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for
25 example sodium carboxymethylcellulose, methylcellulose, hydropropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting agents may be a naturally-occurring phosphatide, for example, lecithin, or condensation products of an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example
30 heptadecaethyleneoxycetanol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more preservatives, for example ethyl, or n-propyl p-

hydroxybenzoate, one or more coloring agents, one or more flavoring agents, and one or more sweetening agents, such as sucrose or saccharin.

Oily suspensions may be formulated by suspending the active ingredients in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavoring agents may be added to provide palatable oral preparations. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active ingredient in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example sweetening, flavoring and coloring agents, may also be present.

Pharmaceutical compositions of the invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example olive oil or arachis oil, or a mineral oil, for example liquid paraffin or mixtures of these. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol, anhydrides, for example sorbitan monooleate, and condensation products of the said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavoring agents.

Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, a preservative and flavoring and coloring agents. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known art using those suitable dispersing or wetting agents and suspending agents which have been mentioned above. The sterile injectable preparation may also be sterile injectable solution or suspension in a non-toxic parentally acceptable diluent or solvent, for example as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono-or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

The compounds of general formula I may also be administered in the form of suppositories for rectal administration of the drug. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum to release the drug.

5 Such materials are cocoa butter and polyethylene glycols.

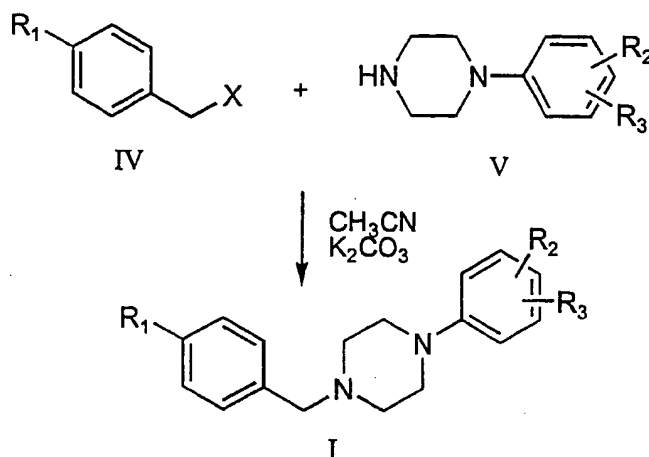
Compounds of general formula I may be administered parenterally in a sterile medium. The drug, depending on the vehicle and concentration used, can either be suspended or dissolved in the vehicle. Advantageously, adjuvants such as local anesthetics, preservatives and buffering agents can be dissolved in the vehicle.

10 Dosage levels of the order of from about 0.1 mg to about 140 mg per kilogram of body weight per day are useful in the treatment of the above-indicated conditions (about 0.5 mg to about 7 g per patient per day). The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration. Dosage unit forms will generally contain
15 between from about 1 mg to about 500 mg of an active ingredient.

It will be understood, however, that the specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, and rate of excretion, drug combination and the severity of the particular
20 disease undergoing therapy.

A representative illustration of methods suitable for the preparation of compounds of the present invention is shown in Schemes I. Those having skill in the art will recognize that the starting materials may be varied and additional steps employed to produce compounds encompassed by the present invention. For example, in certain situations, protection of
25 reactive moieties such as amino groups, will be required.

Preparation of 1-Phenyl-4-Benzylpiperazines



In the above scheme, R₁, R₂ and R₃ are as defined above for formula I.

As shown, a 4-substituted benzyl alkylating agent of general structure IV, possessing
 5 an appropriate leaving group X, is reacted with a 1-phenylpiperazine of general structure V in
 the presence of a suitable base to afford a compound of Formula I as the desired product. The
 leaving group X may be a halogen, a sulfonic acid ester or the like. The reaction is typically
 carried out in a solvent such as acetonitrile with heating at, for example, reflux.

Where they are not commercially available, the compounds of general structures IV
 10 and V may be prepared using known procedures or procedures analogous to those described in
 literature. Those having skill in the art will recognize that the starting materials may be varied
 and additional steps employed to produce compounds encompassed by the present invention.

The disclosures in this application of all articles and references, including patents, are
 incorporated herein by reference.

15 The invention is illustrated further by the following examples which are not to be
 construed as limiting the invention in scope or spirit to the specific procedures and
 compounds described in them.

Example 11-(4-chlorophenyl)-4-(4-chlorobenzyl)piperazine dihydrochloride (Compound 1)

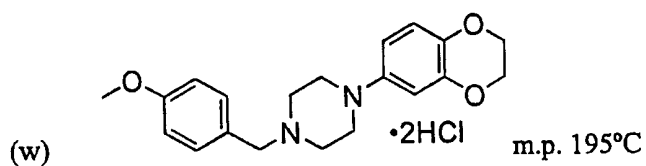
5 A mixture of 1-(4-chlorophenyl)piperazine (1.61 g, 0.01 mole), 4-chlorobenzyl chloride (2.10 g, 0.01 mole) and potassium carbonate (2 g) in acetonitrile (40 mL) is heated at reflux for 6 hours under a nitrogen atmosphere. After cooling, the reaction mixture is poured into water (50 mL) and ether (50 mL). The aqueous layer is discarded and the organic layer is extracted with 1 N aqueous hydrochloric acid solution. The acidic extract is neutralized with
10 6 N ammonium hydroxide solution and extracted with ether. The organic layer is dried (Na_2SO_4) and concentrated to provide the crude free base of the desired unsymmetrically substituted piperazine. This material is dissolved in warm isopropanol (10 mL) and treated with a 1 N solution of HCl in ether until acidic to pH paper. Upon cooling, crystals of dihydrochloride salt are collected (2.2 g, 56 %).

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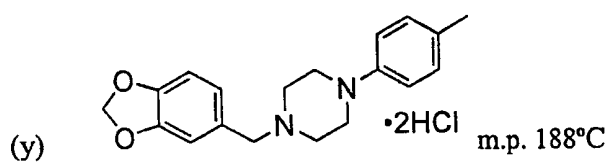
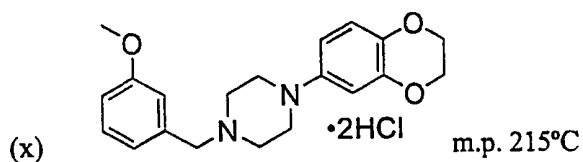
The following compounds are prepared essentially according to procedures set forth above in Example 1.

- (a) 1-(3-chlorophenyl)-4-(4-chlorobenzyl)piperazine dihydrobromide (m.p. 238-240°C)
- (b) 1-(2-chlorophenyl)-4-(4-chlorobenzyl)piperazine dioxalate (m.p. 203-204°C)
- 20 (c) 1-(3, 4-dichlorophenyl)-4-(4-chlorobenzyl)piperazine (m.p. 82-83 °C)
- (d) 1-(4-methylphenyl)-4-(4-chlorobenzyl)piperazine dioxalate (m.p. 204-206°C)
- (e) 1-(3-methylphenyl)-4-(4-chlorobenzyl)piperazine dioxalate (m.p. 233-235°C)
- (f) 1-(2-methylphenyl)-4-(4-chlorobenzyl)piperazine dioxalate (m.p. 205-206°C)
- (g) 1-(3,4-dimethylphenyl)-4-(4-chlorobenzyl)piperazine dihydrochloride. (m.p. 225-
25 228°C, Compound 2)
- (h) 1-(4-methoxyphenyl)-4-(4-chlorobenzyl)piperazine dioxalate (m.p. 211-212°C, Compound 3)
- (i) 1-(3-methoxyphenyl)-4-(4-chlorobenzyl)piperazine dioxalate (m.p. 205-207°C)
- (j) 1-(2-methoxyphenyl)-4-(4-chlorobenzyl)piperazine dioxalate (m.p. 217-220 °C)
- 30 (k) 1-(4-ethoxyphenyl)-4-(4-chlorobenzyl)piperazine dihydrochloride (m.p. 235-237°C)
- (l) 1-(2-ethoxyphenyl)-4-(4-chlorobenzyl)piperazine dihydrobromide (m.p. 215-217°C)
- (m) 1-phenyl-4-(4-chlorobenzyl)piperazine dioxalate (m.p. 228-231°C)
- (n) 1-(4-chlorophenyl)-4-(4-fluorobenzyl)piperazine dihydrobromide
- (o) 1-(4-chlorophenyl)-4-(4-methylbenzyl)piperazine dihydrobromide (Compound 4)

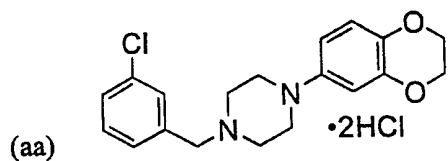
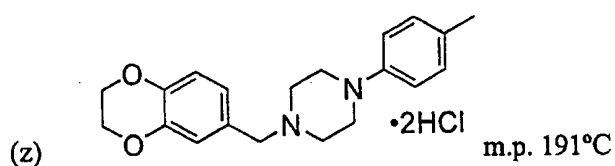
- (p) 1-(3-chlorophenyl)-4-(4-methylbenzyl)piperazine dioxalate (m.p. 199-200°C)
 (q) 1-(4-chlorophenyl)-4-(4-methylbenzyl)piperazine dioxalate (m.p. 219-221°C)
 (r) 1-(3, 4-dichlorophenyl)-4-(4-methylbenzyl)piperazine dihydrobromide
 (s) 1-(4-methylphenyl)-4-(4-methylbenzyl)piperazine dioxalate (m.p. 203-204°C)
 5 (t) 1-(2-methylphenyl)-4-(4-methylbenzyl)piperazine dioxalate (m.p. 180-182 °C)
 (u) 1-(4-methoxyphenyl)-4-(4-methylbenzyl)piperazine dihydrobromide
 (v) 1-(2-methoxyphenyl)-4-(4-methylbenzyl)piperazine dihydrobromide (m.p. 234-235°C)



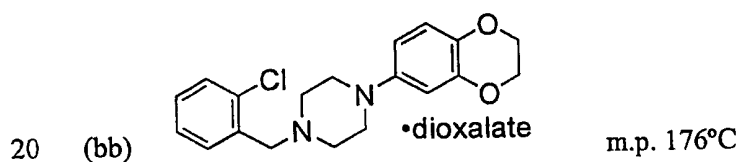
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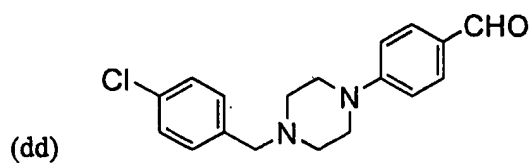
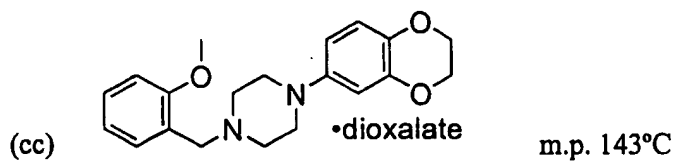


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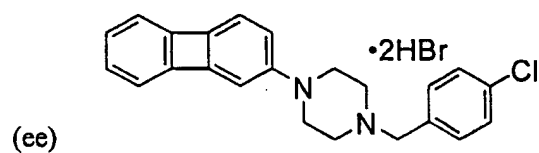


receptor binding in above assays (nm): D4: 900; D3: 6300; D2: 4166

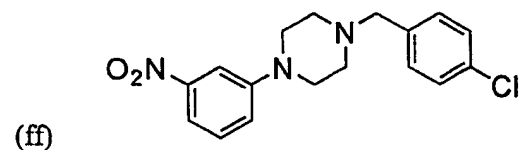




5 receptor binding in D4 assay described above: 50nm

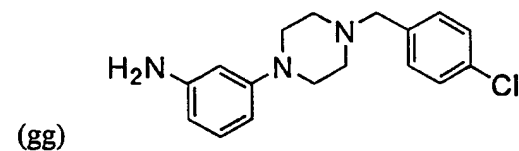


10 receptor binding in D4 assay described above: 554nm

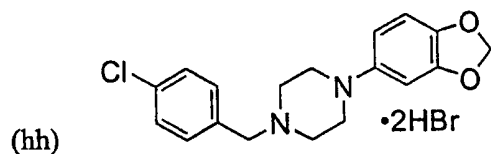


receptor binding in assays described above: D4: 47; D2: 447nm

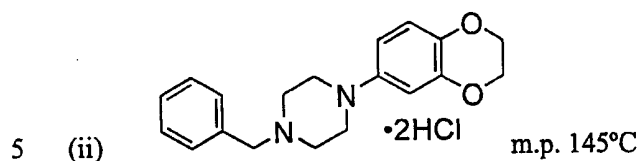
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receptor binding in assays described above: D4: 37; D2: 1730



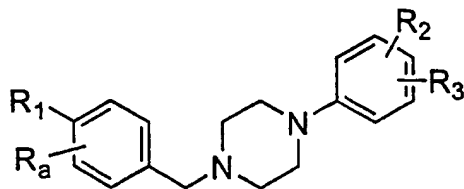
receptor binding in assays described above: D4: 6; D2: 10,000



The invention and the manner and process of making and using it, are now described in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, to make and use the same. It is to be understood that the foregoing describes preferred embodiments of the present invention and that modifications may be made therein without departing from the spirit or scope of the present invention as set forth in the claims. To particularly point out and distinctly claim the subject matter regarded as invention, the following claims conclude this specification.

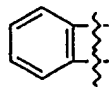
What is claimed is:

1. A compounds of the formula:



or the pharmaceutically acceptable acid salts thereof wherein:

- 5 R_1 is halogen or C_1 - C_4 alkyl, and R_a is hydrogen; or
 R_1 and R_a together represent C_{3-5} alkylene containing one or two oxygen atoms which together with the phenyl group forms a five- or six-membered ring containing one or two oxygen atoms; or

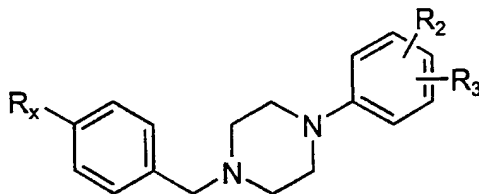


R_1 and R_a together represent

- 10 R_2 and R_3 are the same or different and represent hydrogen, halogen, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, alkylthio, hydroxy, nitro, amino, monoalkylamino or dialkylamino, or
 R_2 and R_3 together represent C_{3-5} alkylene or alkenylene containing one or two oxygen atoms which together with the phenyl form a five- or six-membered ring substituted with one or two oxygen atoms,
 15 with the proviso that R_2 and R_3 may not be 2-isopropoxyl and hydrogen respectively when R_1 is bromo.

2. A compound according to Claim 1, wherein R_1 is methyl.

- 20 3. A compound of the formula:



or the pharmaceutically acceptable salts thereof wherein

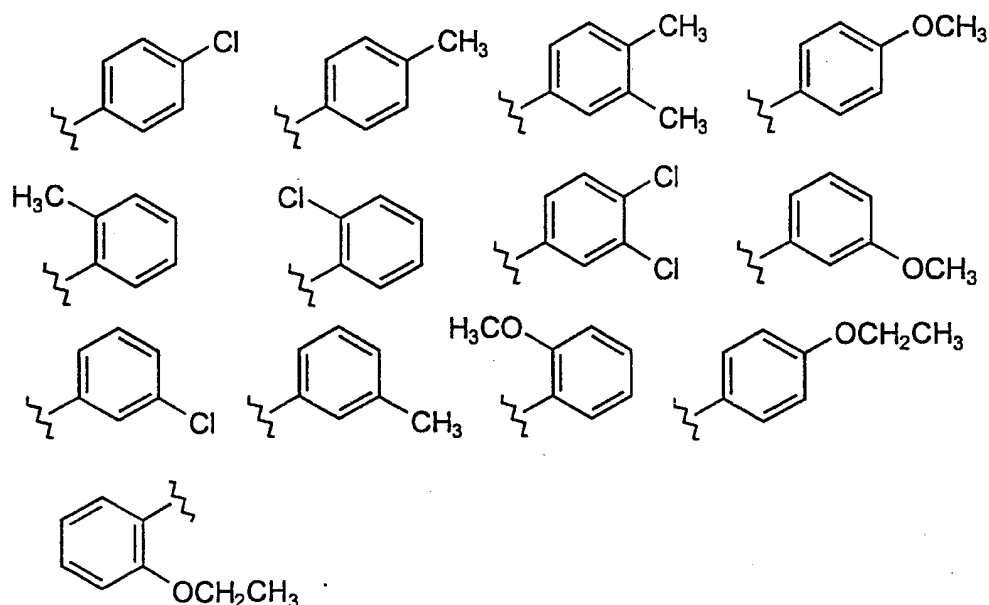
R_x is fluorine, chlorine, bromine, or iodine; and

- 25 R_2 and R_3 are the same or different and represent hydrogen, halogen, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, alkylthio, hydroxy, amino, monoalkylamino or dialkylamino.

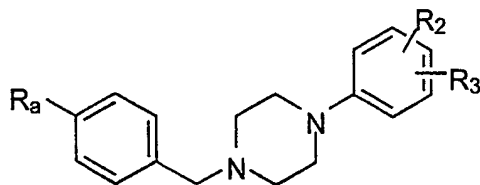
4. A compound according to Claim 3, wherein R_2 and R_3 may not be 2-isopropoxyl and hydrogen, respectively, when R_1 is bromo.

5. A compound according to claim 3, wherein R_x is chloride; R_2 and R_3 may not be 2-isopropoxyl and hydrogen, respectively, when R_1 is bromo; R_2 is chloride, methyl or methoxy; and R_3 is hydrogen or methyl.

6. A compound according to claim 5, wherein the phenyl group substituted with R_2 and R_3 is selected from the group consisting of:



7. A compound of the formula:

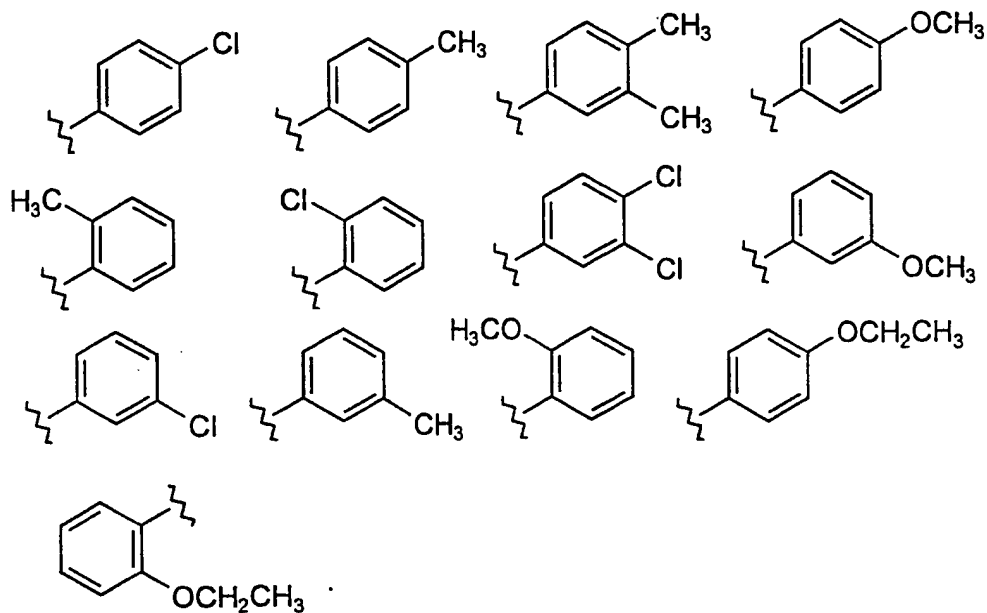


15 or the pharmaceutically acceptable salts thereof wherein

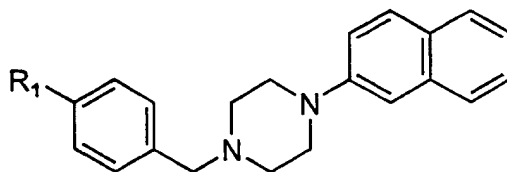
R_a is C_1 - C_4 alkyl; and

R_2 and R_3 are the same or different and represent hydrogen, halogen, C_1 - C_4 alkyl, C_1 - C_4 alkoxy, alkylthio, hydroxy, amino, monoalkylamino or dialkylamino.

8. A compound according to Claim 7, wherein R_1 is methyl.
9. A compound of according to Claim 7, wherein R_2 is chloride, fluoride, methyl or methoxy; and R_3 is hydrogen or methyl.
10. A compound according to claim 8, wherein the phenyl group substituted with R_2 and R_3 is selected from the group consisting of:



11. A compound of the formula:



or the pharmaceutically acceptable salts thereof wherein:

R_1 is C_1 - C_4 alkyl or halogen.

12. A compound according to Claim 11, wherein R_1 is chloro.

13. A compound according to Claim 1, which is 1-(3-chlorophenyl)-4-(4-chlorobenzyl)piperazine.

14. A compound according to Claim 1, which is 1-(2-chlorophenyl)-4-(4-chlorobenzyl)piperazine.

15. A compound according to Claim 1, which is 1-(3, 4-dichlorophenyl)-4-(4-chlorobenzyl)piperazine.

16. A compound according to Claim 1, which is 1-(4-methylphenyl)-4-(4-chlorobenzyl)piperazine.

17. A compound according to Claim 1, which is 1-(3-methylphenyl)-4-(4-chlorobenzyl)piperazine.

18. A compound according to Claim 1, which is 1-(2-methylphenyl)-4-(4-chlorobenzyl)piperazine.

19. A compound according to Claim 1, which is 1-(3,4-dimethylphenyl)-4-(4-chlorobenzyl)piperazine dihydrobromide.

20. A compound according to Claim 1, which is 1-(4-methoxyphenyl)-4-(4-chlorobenzyl)piperazine dihydrobromide.

21. A compound according to Claim 1, which is 1-(3-methoxyphenyl)-4-(4-chlorobenzyl)piperazine.

22. A compound according to Claim 1, which is 1-(2-methoxyphenyl)-4-(4-chlorobenzyl)piperazine.

23. A compound according to Claim 1, which is 1-(4-ethoxyphenyl)-4-(4-chlorobenzyl)piperazine.

24. A compound according to Claim 1, which is 1-(2-ethoxyphenyl)-4-(4-chlorobenzyl)piperazine.

25. A compound according to Claim 1, which is 1-phenyl-4-(4-chlorobenzyl)piperazine.

26. A compound according to Claim 1, which is 1-(4-chlorophenyl)-4-(4-fluorobenzyl)piperazine.

27. A compound according to Claim 1, which is 1-(4-chlorophenyl)-4-(4-methylbenzyl)piperazine.

28. A compound according to Claim 1, which is 1-(3-chlorophenyl)-4-(4-methylbenzyl)piperazine.

29. A compound according to Claim 1, which is 1-(3, 4-dichlorophenyl)-4-(4-methylbenzyl)piperazine.

30. A compound according to Claim 1, which is 1-(4-methylphenyl)-4-(4-methylbenzyl)piperazine.

31. A compound according to Claim 1, which is 1-(2-methylphenyl)-4-(4-methylbenzyl)piperazine.

32. A compound according to Claim 1, which is 1-(4-methoxyphenyl)-4-(4-methylbenzyl)piperazine.

33. A compound according to Claim 1, which is 1-(2-methoxyphenyl)-4-(4-methylbenzyl)piperazine.

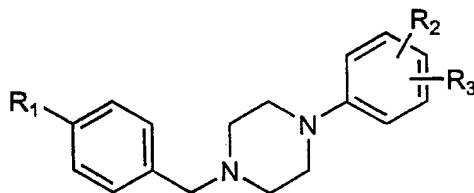
34. A method for treating or preventing neuropsychological disorders which comprises administering to a patient in need of such treatment a compound selected from the group consisting of

- (a) 1-(3-chlorophenyl)-4-(4-chlorobenzyl)piperazine;
- (b) 1-(2-chlorophenyl)-4-(4-chlorobenzyl)piperazine;
- (c) 1-(3, 4-dichlorophenyl)-4-(4-chlorobenzyl)piperazine;
- (d) 1-(4-methylphenyl)-4-(4-chlorobenzyl)piperazine;

- (e) 1-(3-methylphenyl)-4-(4-chlorobenzyl)piperazine;
 (f) 1-(2-methylphenyl)-4-(4-chlorobenzyl)piperazine;
 (g) 1-(3,4-dimethylphenyl)-4-(4-chlorobenzyl)piperazine;
 (h) 1-(4-methoxyphenyl)-4-(4-chlorobenzyl)piperazine;
 5 (i) 1-(3-methoxyphenyl)-4-(4-chlorobenzyl)piperazine;
 (j) 1-(2-methoxyphenyl)-4-(4-chlorobenzyl)piperazine;
 (k) 1-(4-ethoxyphenyl)-4-(4-chlorobenzyl)piperazine;
 (l) 1-(2-ethoxyphenyl)-4-(4-chlorobenzyl)piperazine;
 (m) 1-phenyl-4-(4-chlorobenzyl)piperazine;
 10 (n) 1-(4-chlorophenyl)-4-(4-fluorobenzyl)piperazine;
 (o) 1-(4-chlorophenyl)-4-(4-methylbenzyl)piperazine;
 (p) 1-(3-chlorophenyl)-4-(4-methylbenzyl)piperazine;
 (q) 1-(4-chlorophenyl)-4-(4-methylbenzyl)piperazine;
 (r) 1-(3,4-dichlorophenyl)-4-(4-methylbenzyl)piperazine;
 15 (s) 1-(4-methylphenyl)-4-(4-methylbenzyl)piperazine;
 (t) 1-(2-methylphenyl)-4-(4-methylbenzyl)piperazine;
 (u) 1-(4-methoxyphenyl)-4-(4-methylbenzyl)piperazine;
 (v) 1-(2-methoxyphenyl)-4-(4-methylbenzyl)piperazine;
 (w) 1-(4-chlorophenyl)-4-(4-chlorobenzyl)piperazine dihydrochloride; and
 20 (x) 1-(2-isopropoxyphenyl)-4-(4-bromobenzyl)piperazine.

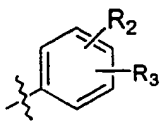
35. A compound according to Claim 1, which is 1-Naphthyl-4-(4-chlorobenzyl)piperazine.

- 25 36. A compound of the formula:

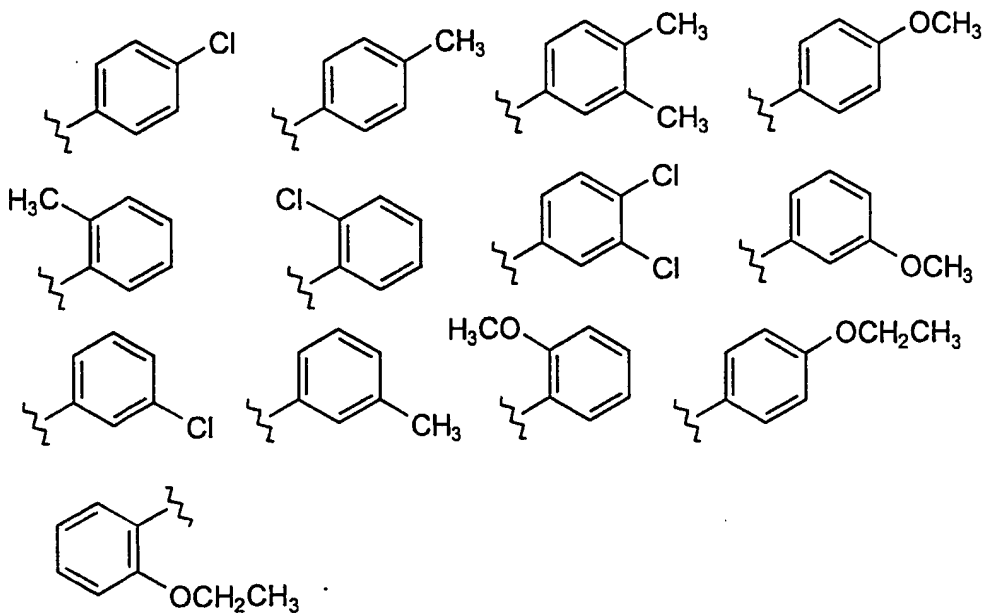


or the pharmaceutically acceptable salts thereof wherein:

R₁ is chlorine, fluorine, or methyl; and

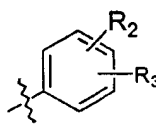


is selected from the group consisting of:

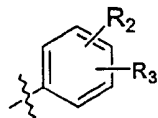


- 5 37. A compound according to claim 36, wherein R₁ is Cl.
38. A compound according to claim 36, wherein R₁ is F.
39. A compound according to claim 36, wherein R₁ is methyl.

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40. A compound according to claim 37, wherein  is 4-chlorophenyl or 4-methoxyphenyl.

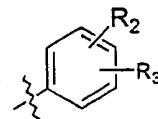
41. A compound according to claim 38, wherein



is 4-methylphenyl,

4-chlorophenyl, or 4-methoxyphenyl.

42. A compound according to claim 39, wherein

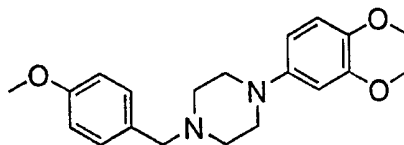


is 4-ethoxyphenyl,

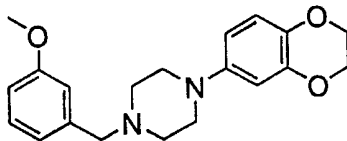
4-methylphenyl, or 4-chlorophenyl.

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43. A compound according to Claim 1, which is

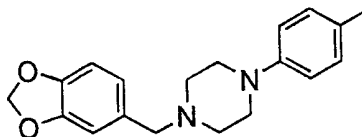


44. A compound according to Claim 1, which is



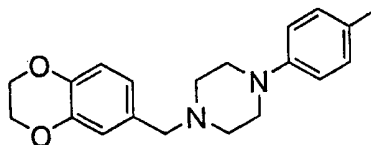
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45. A compound according to Claim 1, which is

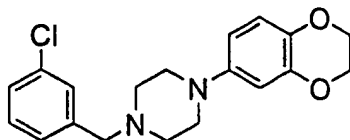


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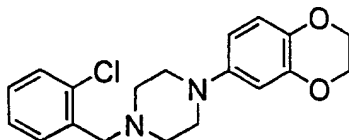
46. A compound according to Claim 1, which is



47. A compound according to Claim 1, which is

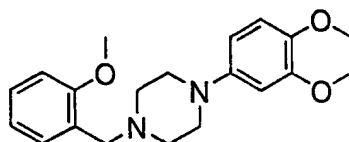


48. A compound according to Claim 1, which is

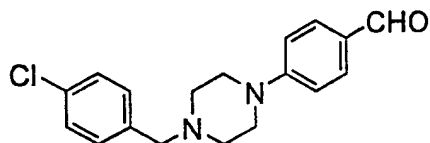


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49. A compound according to Claim 1, which is

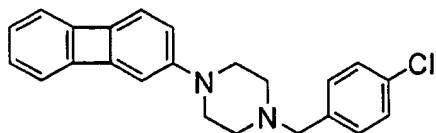


50. A compound according to Claim 1, which is



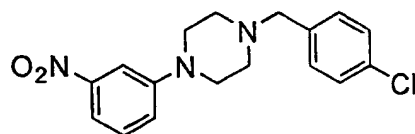
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51. A compound according to Claim 1, which is

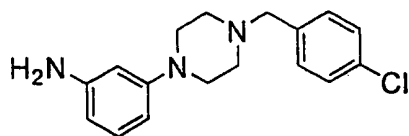


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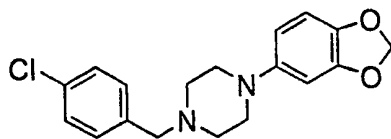
52. A compound according to Claim 1, which is



53. A compound according to Claim 1, which is

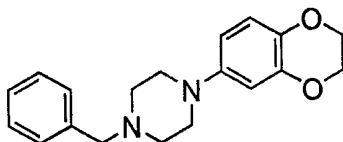


54. A compound according to Claim 1, which is



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55. A compound according to Claim 1, which is



INTERNATIONAL SEARCH REPORT

In 21 Application No
PCT/US 98/01628

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07D295/06 A61K31/495 C07D405/10

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SARATI, S. ET AL.: "Kinetics of PIREBEDIL and effects on dopamine metabolism: hepatic biotransformation is not a determinant of its dopaminergic action in rats" PSYCHOPHARMACOLOGY, vol. 105, 1991, BERLIN, pages 541-545. XP002065935 see the whole document ---	1-33, 35-55
Y	US 4 260 610 A (REGNIER GILBERT ET AL) 7 April 1981 see the whole document ---	1-33, 35-55
Y	US 3 299 067 A (REGNIER, G. ET AL.) 17 January 1967 see the whole document ---	1-33, 35-55
-/--		



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

Special categories of cited documents

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- S" document member of the same patent family

Date of the actual completion of the international search

27 May 1998

Date of mailing of the international search report

19/06/1998

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Authorized officer

Stellmach, J

INTERNATIONAL SEARCH REPORT

Int. Application No
PCT/US 98/01628

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	BOYFIELD, I. ET AL.: "N-(Substituted-phenyl)-piperazines: Antagonists with high Binding and Functional Selectivity for Dopamine D4 Receptors" BIOORG. & MED. CHEM. LETT., vol. 6, no. 11, 1996, OXFORD, pages 1227-1232, XP002065936 see the whole document ---	1-33, 35-55
Y	EP 0 574 271 A (MCNEILAB INC) 15 December 1993 see the whole document ---	1-33, 35-55
Y	REITZ, A.B. ET AL.: "N-Aryl-N'-Benzylpiperazines as Potential Antipsychotic Agents" J. MED. CHEM., vol. 38, no. 21, 1995, WASHINGTON, pages 4211-4222, XP002065378 * see page 4215, table 3 * see the whole document ---	1-33, 35-55
Y	WO 93 04684 A (MCNEILAB INC) 18 March 1993 cited in the application see the whole document ---	1-33, 35-55
Y	WO 93 04682 A (MCNEILAB INC) 18 March 1993 see the whole document ---	1-33, 35-55
Y	WO 94 06768 A (MCNEILAB INC) 31 March 1994 see the whole document ---	1-33, 35-55
Y	HADLEY M S: "D4 RECEPTORS AND THEIR ANTAGONISTS" MEDICINAL RESEARCH REVIEWS, vol. 16, no. 6, 1996, pages 507-526, XP000654693 * see page 521, fig. 4 * see the whole document ---	1-33, 35-55
Y	WO 94 20471 A (MERCK SHARP & DOHME ; KULAGOWSKI JANUSZ JOZEF (GB); LEESON PAUL DAV) 15 September 1994 see the whole document ---	1-33, 35-55
	-/--	

INTERNATIONAL SEARCH REPORT

Int'l Application No
PCT/US 98/01628

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	<p>MACH, R.H. ET AL.: "The use of '¹⁸F!4-Fluorobenzyl Iodide (FBI) in PET Radiotracer Synthesis : Model Alkylation Studies and Its Application in the Design of Dopamine D1 and D2 Receptor-based Imaging Agents" NUCL.MED.BIOL., vol. 20, no. 6, 1993, OXFORD, pages 777-794, XP002065565 cited in the application see the whole document ---</p>	<p>1-33, 35-55</p>
A	<p>PRASAD R N ET AL: "POTENTIAL ANTIHYPERTENSIVE AGENTS. II. UNSYMMETRICALLY 1,4-DISUBSTITUTED PIPERAZINES. I" JOURNAL OF MEDICINAL CHEMISTRY, vol. 11, no. 6, November 1968, pages 1144-1150, XP002036253 cited in the application see the whole document ---</p>	<p>1-33, 35-55</p>
P,X	<p>WO 97 41108 A (WARNER LAMBERT CO ;GLASE SHELLY ANN (US); PURCHASE TERRI STOEBER ()) 6 November 1997 see the whole document -----</p>	<p>1-33, 35-55</p>

INTERNATIONAL SEARCH REPORT

Information on patent family members

In International Application No

PCT/US 98/01628

Patent document cited in search report		Publication date	Patent family members)	Publication date
US 4260610	A	07-04-1981	AR 220730 A	28-11-1980
			AR 220793 A	28-11-1980
			AR 220794 A	28-11-1980
			AU 4140778 A	17-05-1979
			BE 871857 A	08-05-1979
			CA 1117944 A	09-02-1982
			DE 2848139 A	10-05-1979
			FR 2408605 A	08-06-1979
			GB 2009732 A,B	20-06-1979
			NL 7811135 A	11-05-1979
			OA 6083 A	30-06-1981
			ZA 7806262 A	31-10-1979
US 3299067	A	17-01-1967	BE 655431 A	06-05-1965
			DE 1297610 B	
			DK 115995 B	01-12-1969
			FI 46163 B	02-10-1972
			FR 4770 M	
			FR 1451232 A	03-12-1966
			GB 1101425 A	
			NL 127996 C	
			NL 6413349 A	20-05-1965
			SE 322521 B	13-04-1970
EP 0574271	A	15-12-1993	US 5332743 A	26-07-1994
			AU 664093 B	02-11-1995
			CA 2098140 A	13-12-1993
			FI 932691 A	13-12-1993
			JP 6271538 A	27-09-1994
			NO 932158 A	13-12-1993
			NZ 247787 A	26-10-1995
WO 9304684	A	18-03-1993	AU 1363392 A	05-04-1993
			AU 657799 B	23-03-1995
			AU 2659992 A	05-04-1993
			CA 2095826 A	12-03-1993
			CA 2095847 A	12-03-1993
			EP 0562049 A	29-09-1993
			EP 0563345 A	06-10-1993
			FI 932103 A	10-05-1993

INTERNATIONAL SEARCH REPORT

Information on patent family members

In International Application No

PCT/US 98/01628

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9304684 A		FI 932104 A	10-05-1993
		HU 64535 A	28-01-1994
		HU 68963 A	28-08-1995
		JP 6502870 T	31-03-1994
		JP 6502183 T	10-03-1994
		MX 9102407 A	31-05-1994
		NZ 240863 A	27-04-1995
		PT 99700 A	31-03-1993
		WO 9304682 A	18-03-1993
		US 5569659 A	29-10-1996
		ZA 9109629 A	06-12-1993
WO 9304682 A	18-03-1993	AU 1363392 A	05-04-1993
		AU 657799 B	23-03-1995
		AU 2659992 A	05-04-1993
		CA 2095826 A	12-03-1993
		CA 2095847 A	12-03-1993
		EP 0562049 A	29-09-1993
		EP 0563345 A	06-10-1993
		FI 932103 A	10-05-1993
		FI 932104 A	10-05-1993
		HU 64535 A	28-01-1994
		HU 68963 A	28-08-1995
		JP 6502870 T	31-03-1994
		JP 6502183 T	10-03-1994
		MX 9102407 A	31-05-1994
		NZ 240863 A	27-04-1995
		PT 99700 A	31-03-1993
		WO 9304684 A	18-03-1993
		US 5569659 A	29-10-1996
		ZA 9109629 A	06-12-1993
WO 9406768 A	31-03-1994	US 5314885 A	24-05-1994
		AT 153657 T	15-06-1997
		AU 679187 B	26-06-1997
		AU 4856293 A	12-04-1994
		CA 2144344 A	31-03-1994
		DE 69311123 D	03-07-1997
		DE 69311123 T	06-11-1997
		DK 660822 T	25-08-1997

INTERNATIONAL SEARCH REPORT

Information on patent family members

In: 31 Application No

PCT/US 98/01628

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9406768 A		EP 0660822 A ES 2104174 T JP 8501548 T NZ 256263 A US 5449677 A	05-07-1995 01-10-1997 20-02-1996 26-01-1996 12-09-1995
WO 9420471 A	15-09-1994	AU 679042 B AU 6113294 A CA 2156409 A EP 0687255 A JP 8508466 T US 5607946 A	19-06-1997 26-09-1994 15-09-1994 20-12-1995 10-09-1996 04-03-1997
WO 9741108 A	06-11-1997	AU 2446297 A	19-11-1997